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Characteristics associated with significantly worse quality of life in mycosis fungoides/Sézary syndrome from the Prospective Cutaneous Lymphoma International Prognostic Index (PROCLIPI) study

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Abstract

Background: Mycosis fungoides (MF) and Sézary Syndrome (SS) are the most common cutaneous T-cell lymphomas. MF/SS is accompanied by considerable morbidity from pain, itching and disfigurement.

Aim: To identify factors associated with poorer health-related quality of life (HRQoL) in newly diagnosed MF/SS patients.

Methods: Patients enrolled into PROCLIPI (an international observational study in MF/SS) had HRQoL assessed using the Skindex-29 questionnaire. Skindex-29 scores were analysed in relation to patient-specific and disease-specific characteristics.

Results: The study population consisted of 237 patients (60.3% male) with a median age of 60 years (IQR 49-70yrs), of whom 179 had early MF and 58 had advanced MF/SS. In univariate analysis, HRQoL as measured by Skindex-29 was worse in females, SS, late-stage MF, those with elevated LDH, alopecia, high mSWAT and confluent erythema. Linear regression models only identified female gender (β*=8.61, p=0.003*) and alopecia (β*=9.71, p=0.02*) as independent predictors for worse global HRQoL. In item-level analysis showed that the severe impairment in symptoms (OR 2.14, 95% CI 1.19-3.89) and emotions (OR 1.88, 95% CI 1.09-3.27) subscale scores seen in female patients was caused by more burning/stinging, pruritus, irritation and greater feelings of depression, shame, embarrassment and annoyance with their diagnosis of MF/SS.

Conclusion: HRQoL is significantly more impaired in newly diagnosed female patients with MF/SS and in those with alopecia. As Skindex-29 does not include existential questions on cancer which may cause additional worry and distress, a comprehensive validated CTCL specific questionnaire is urgently needed to more accurately assess disease-specific HRQoL among these patients.

What is already known about this topic?

- Cross-sectional studies of mixed populations of known and newly diagnosed MF/SS patients have shown significant impairment of HRQoL.
- Previous studies on assessing gender-specific differences in HRQoL in MF/SS are conflicting.
- More advanced stage disease and pruritus is associated with poorer HRQoL in MF/SS.

What does this study add?

- This is the first prospective study investigating HRQoL in a homogenous group of only newly diagnosed MF/SS patients.
- In newly diagnosed MF/SS patients, HRQoL in is worse females and in those with alopecia and confluent erythema.
- MF/SS diagnosis has a multi-dimensional impact on patient HRQoL including a large burden of cutaneous symptoms as well as negative impact on the emotional well-being.

Introduction

Cutaneous T cell lymphomas (CTCLs) are a heterogeneous group of non-Hodgkin lymphomas characterized by skin homing T-cells. Mycosis fungoides (MF) is the most common subtype of CTCL (54-72% of all cases) and has an annual incidence 7.7 new cases per 1,000,000 person-years with a median age at diagnosis of 55-60 years and more commonly affects male patients (M:F = 2.1:1)[1]. Early-stage classical MF is characterized by erythematous, scaly patches or plaques involving photo-protected limb girdle sites (so-called 'bathing trunk' distribution). Sézary syndrome (SS) representing 3% of CTCLs, is an aggressive leukaemic form of cutaneous lymphoma typically characterized by erythroderma, generalised lymphadenopathy and peripheral blood involvement[2,3].

The 2007 revised staging system of MF/SS classify disease presentation based on skin (T), lymph node (N), visceral (M) and blood (B) involvement[4]. Early-stage disease (IA to IIA) carries a good prognosis with a median survival of 12.9 years, in contrast to late-stage disease (IIB to IVB) which carries a worse prognosis[5]. The predicted 5-year overall survival (OS) rates are 57.4% for stage IIB, 58.2% for stage III, 42.9% for stage IVA, and 39% for stage IVB. Stage IV disease, age >60 years, large cell transformation (LCT; presence of large cells exceeding 25% of the total lymphoid infiltrate) and elevated serum lactate dehydrogenase (LDH) are independent prognostic factors for worse survival[6].

Quality of life (QoL) is a broad concept incorporating all aspects of an individual's existence, while health-related quality of life (HRQoL) is a subset of QoL that relates more specifically to the effects health/illness(es)[7]. While QoL and HRQoL are used interchangeably and synonymously in the literature, both aim to capture patient health and well-being[8]. Previous studies have found HRQoL is significantly impaired in CTCL however it is not routinely assessed in daily clinical practice and hence treating physicians may be unaware of patients at risk for social isolation and depression. The PROCLIPI (Prospective Cutaneous Lymphoma International Prognostic Index) study[9] provides a unique platform to study HRQoL in patients with MF/SS.

The aim of this observational multicentre study was to evaluate the effects of skin disease on HRQoL in patients with MF/SS enrolled in the PROCLIPI study using the Skindex-29 HRQoL instrument[10].

Methods

Study Design

The PROCLIPI study prospectively collects clinical, pathological, genotypic, treatment and HRQoL data on MF/SS from worldwide sites[9]. All newly diagnosed patients with MF/SS are eligible for study participation within 6 months of a multidisciplinary confirmed diagnosis. The datasets collected at baseline and stage progression are shown in Figure S1 (Supplementary Data). HRQoL was captured using the Skindex-29 questionnaire. The study was approved by the local Institutional Review Board/Research Ethic Committees (IRB/REC) of each institution and all patients provided written informed consent.

Skindex-29 Questionnaire

HRQoL data were recorded on paper using the Skindex-29 questionnaire (permission granted by MAPI Research Trust, Lyon, France, November 2014)[11] in the native language of the patient and subsequently uploaded to the PROCLIPI database. For this work, only Skindex-29 questionnaires at diagnosis (visit 1) were included.

The Skindex-29 questionnaire is a 30-item questionnaire refined from the original 61 item version of the Skindex dermatologic HRQoL instrument[10] with one item (item 18) excluded from scoring[12]. The 29 items deal with various aspects of HRQoL including 7 subscale items relating physical symptoms, 10 relating to emotional aspects of the disease and 12 relating to psychosocial functioning. Each statement in the Skindex-29 questionnaire was scored on a 5-point Likert scale (points;never=1,rarely=2,sometimes=3,often=4,all-the-time=5). Participant's answers were converted into linear scale scores between 0 (no effect) to 100 (maximum effect), with higher scale scores indicating a lower HRQoL[10]. The respondent's overall HRQoL was expressed as a global Skindex-29 score by computing the mean of the points from each subscale[13]. Global Skindex-29 scores were excluded if >25% of items were missing.

Statistical Analysis

Data was collated and analysed at Biostatistical Department, University Hospital Birmingham, UK. Normality of distribution was verified using the Shapiro-Wilk test. Univariate analyses were performed between Skindex-29 median scores and groups of patients according to patient characteristics (age, gender, ECOG) and disease characteristics (MF/SS, EORTC classification, early vs late-stage, TNMB stage, disease stage, raised LDH and clinical features including alopecia, confluent erythema, hypopigmentation, ulceration and follicular MF lesions). The Mann-Whitney U-test and Kruskal-Wallis test (followed by Bonferroni correction for multiple comparisons) was used to analyze continuous variables and are presented as medians and interquartile ranges (IQR). The power and direction of the relationships between age, mSWAT and Skindex-29 scores was determined using the non-parametric Spearman's rank-order correlation. The association between categorical variables was assessed by Chi-square ($\chi 2$) test.

Multiple linear regression analysis was completed using Skindex-29 scores as the dependent variable whereas independent variables collected at the same timepoint included demographic data (age and gender), diagnosis of MF/SS, early (IA-IIA)/late-stage disease (IIB-IVB), alopecia and confluent erythema. In addition, the role of each aforementioned independent variables on HRQoL were evaluated in a logistic regression model on the basis of Skinex-29 score dichotomized as severe or non-severe HRQoL impairment as the dependent variable. The cut-off scores for severe HRQoL impairment defined by Prinsen et al for global Skindex-29 score was ≥44 and for symptoms, ≥52 emotions, ≥39 and functioning, ≥37[14].

To further explore specific items in the Skindex-29 questionnaire relating to worse HRQoL, an item-level analysis was conducted using ordinal regression analysis[15]. Association between age, gender, MF/SS, early/late-stage disease, alopecia and confluent erythema in determining item responses were evaluated based on the Skindex-29 questionnaire likert scale. Results are reported as odds ratio (OR) and 95% confidence intervals (CI).

All analyses were carried out using R version 3.2.4 with a level of significance set at $p < 0.05$.

Results

From July'15-Dec'18, Skindex-29 scores in 238 patients from 25 specialist centres spanning 4 continents (UK, n=110; Belgium, n=20; Austria, n=18; Greece, n=13; France, n=11; Spain, n=11; Italy, n=10; USA, n=9; Finland, n=8; Australia, n=8; Germany, n=8; Switzerland, n=6; Hungary, n=3 and Brazil, n=2) (Table 1) were collected. Of the 238 patient questionnaires, n=207 (86.97%) were 100% complete, while n=21 (8.82%) had only one missing response. Five patients (2.1%) had two missing responses and four patients (1.68%) had three missing responses while one was excluded from final analysis due to 10 missing responses. In our final study population (n=237), the median age was 60 years (IQR 49-70) with a male to female ratio of 1.5:1. A total of 211 (89.03%) patients had MF (early-stage, n=178; late-stage, n=33) and 26 (10.97%) had SS. The male to female ratio was 1.58:1 in early-stage MF and 1.36:1 in late-stage MF/SS ($\chi 2$ test, p=0.62). The median global Skindex-29 score for the study population was 29.75 (IQR 15.44 - 47.21) (Table 2).

Variables associated with worse HRQoL in patients with MF/SS

No correlation between global Skindex-29 score and patient age (p=0.83) or ECOG performance status (p=0.23) was observed (Table 3). Female patients had significantly worse HRQoL (p=0.02) with higher median (IQR) global Skindex-29 scores [34.19 (IQR 20.69-52.84)] compared to male patients [27.62 (IQR 13.73-44.87)]. A corresponding gender disparity in QoL was observed in both symptoms (p=0.01) and emotions (p=0.02) but not in functioning subscales (p=0.12).

HRQoL correlated with extent of skin disease as measured by mSWAT score (*P*<0.0001, Table 3) and T stage. Interestingly, the extent of blood involvement but not nodal or visceral involvement was significantly associated with impaired overall HRQoL (Supplementary data, Table S1). When patients were stratified according to MF/SS diagnosis, patients diagnosed with SS had significantly more impaired overall HRQoL (p=0.001) in all subscale domains compared to MF. Given that more advanced disease is associated with a greater burden of symptoms HRQoL was evaluated in patients with early (IA-IIA) and late stages (IIB-IVB). Patients with late-stage disease had worse overall HRQoL (p=0.002), more symptoms (p=0.0002) and functional impairment (p=0.002) in contrast to those with early-stage disease. As more advanced disease is characterized by a greater burden of cutaneous and extra-cutaneous disease, the impact of serum LDH on HRQoL was examined. Global Skindex-29 scores were more significantly impaired in patients with elevated LDH (p=0.001) compared to those with normal levels. This was also true for symptoms and functioning subscale scores whereas a non-significant trend in emotional subscale scores (p=0.05) in patients with a raised LDH was observed.

Examination of clinical features in patients with MF/SS demonstrated that patients with alopecia had worse global (p=0.004), emotional (p=0.001) and functioning (p=0.03) subscale scores but not symptoms (p=0.05) scores compared to those without alopecia. Patients with confluent erythema had worse overall HRQoL but no differences in emotional subscale scores were found. In those with confluent erythema there was a moderate correlation between mSWAT and symptom subscale scores (r_s=0.53; 95% CI 0.20-0.75, p=0.002) but only a weak correlation with global and functioning subscale scores (Supplementary file, Table S1). No significant difference in HRQoL was observed in patients with hypopigmentation, ulceration or follicular MF lesions.

Independent Factors Associated with Worse HRQoL

To determine which parameters were independently associated with worse HRQoL in MF/SS, a number of candidate covariates were computed in multivariate linear regression models using Skindex-29 scores as the dependent variable. Independent factors associated with worse global Skindex-29 scores included female gender [β=8.61 (95% CI, 2.89-14.09); p=0.003], alopecia [β=9.71 (95% CI, 1.63-17.44); p=0.02] and confluent erythema [β=8.13 (95% CI, -0.02-16.06); p=0.05]. Female gender and confluent erythema had a significant relationship with worse symptoms and functioning, whereas only a diagnosis of alopecia was related to overall impairment of emotions [β=12.7 (95% CI, 3.56- 21.42); p=0.01] (Table 4).

In a logistic model using severe impairment of HRQoL (global, symptoms, emotions and functioning cut-offs were $\geq$44, $\geq$52, $\geq$39 and $\geq$37) as the dependent variable, female gender was associated with severe impairment in symptoms (OR 2.14, 95% CI 1.19-3.89, p=0.01) and emotions (OR 1.88, 95% CI 1.09-3.27, p=0.02) subscale scores. Confluent erythema was associated with severe impairment of symptoms (OR 2.8, 95% CI 1.26-6.24, p=0.01) and alopecia with the emotional subscale (OR 2.57, 95% CI 1.18-5.79 p=0.02) [Supplementary file, Table S2].

Item-analysis of Skindex-29 questionnaire in MF/SS

An item-level analysis on the Skindex-29 responses was used to identify which answers varied by patient characteristics. Of particular interest were gender specific differences in item responses but also variables such as alopecia, confluent erythema and late-stage disease were assessed. Items on the Skindex-29 questionnaire which were more likely to be scored higher in female patients included subscale questions related to symptoms: burning/stinging, itching, water bothering the skin during bathing/washing, irritation and sensitivity; emotions: depression, shame, embarrassment, annoyance; and functioning: impaired sleep. (Figure 1). Patients with alopecia were more likely to score higher in Skindex-29 items relating to emotions, while patients with confluent erythema were more likely to score higher in questions related to symptoms and functioning. Only one question was significantly more likely in patients with late-stage disease ("my skin condition bleeds") (Supplementary data, Table S3).

Discussion

This is the largest international study to evaluate HRQoL in newly diagnosed MF/SS patients and relating this to patient demographics and physician-reported disease characteristics at the same timepoint. HRQoL was measured using Skindex-29 questionnaire which adequately covers skin disease symptoms but does not include cancer related items. HRQoL in patients with MF/SS was significantly worse in female patients, SS, late-stage MF and those with a raised serum LDH, alopecia and confluent erythema. Both alopecia and confluent erythema are visual clinical features which may impact on a patient's wellbeing. However, in multivariate models only female gender and alopecia were significantly associated with worse global HRQoL. This study highlights the collaborative strength of the PROCLIPI study to provide a unique and meaningful insight into the impact of MF/SS on the lives of affected patients.

There is no standardized approach for the interpretation of Skindex-29 scores. Both distribution-based[16] and anchor-based methods[14] have been used to categorize Skindex-29 scores into mild, moderate and severe. It is generally agreed that an anchor-based approach is the optimal way to determine the minimally important difference (MID) in patient-reported outcomes[17]. Prinsen et al. suggest the cut-offs for mild, moderate, and severe impairment of the global Skindex-29 score to be $\geq$25, $\geq$32 and $\geq$44, respectively[14]. The overall median (IQR) Skindex-29 score reported in our study of 29.75 (15.44 - 47.21) indicates that a diagnosis of MF/SS conveys a mild to moderate impact on overall HRQoL. This is comparable to acne vulgaris, atopic dermatitis, contact dermatitis and psoriasis[13]. Interestingly, the results of our study show that in those with a diagnosis of SS their HRQoL scores are in the severe range [median (IQR) global Skindex-29 score, [50.58 (27.21 - 69.53)] and is much higher than benign dermatoses and non-melanoma skin cancer[13,14]. Importantly, all aspects of HRQoL have been shown to be impaired in patients diagnosed with SS, 58% of whom report pruritus compared with 14% of patients with MF[18]. In logistic regression analysis however, only female gender and confluent erythema were independently associated with worse HRQoL on the symptom subscale indicating a diagnosis of SS alone does not fully explain impaired HRQoL in MF/SS.

In accordance with this finding, we have shown both in univariate and multivariate analysis that female patients with MF/SS had significantly worse HRQoL compared to male patients. Our observed gender differences in HRQoL in MF/SS have been suggested by others[18-20]. One study

reported no gender specific difference in illness perception, but this might have been due to the male predominance within this cohort[20]. Female patients perceive their disease as more chronic and tend to be more emotionally affected than men[19]. We found that female patients have more severe symptoms and are more emotionally affected than men. No overall gender differences in functioning were observed, however the negative impact on sleep observed in female patients may reflect psychological stress. Poorer HRQoL in female patients has been reported both in inflammatory skin diseases such as psoriasis[21], atopic dermatitis[22], vitiligo[23] and also observed in survivors of non-Hodgkin's lymphoma[24].

Our item-analysis of Skindex-29 responses provides insight into those aspects of the disease which are uniquely troublesome for female patients. These included symptoms such as itching, stinging and burning, increased sensitivity and irritation as well as emotional aspects such as shame and embarrassment. Itching is frequently reported by CTCL patients and may be refractory to anti-pruritic medication. Previous studies have shown correlation between pruritus severity score and total Skindex-29 score[25] emphasizing itch as a troublesome symptom[26]. Patients with MF/SS experience a large number of disease related symptoms including pruritus, bleeding, flaking and red skin and an emotional burden of self-consciousness, restricted physical intimacy, anxiety and depression[27,28].

Alopecia was an independent prognostic variable for poorer HRQoL and was present in 14.8% (n=35) of patients in our study, higher than previously reported rates of 2.5% in patients with MF/SS. The most common patterns of MF/SS related alopecia are areata-like patchy loss (33%) and alopecia within MF lesions (67%)[29]. In our observations, alopecia was associated with worse global and symptoms subscale scores and with severe impairment in the emotions subscale score. These findings were substantiated in item analysis showing higher responses that included shame, worry, anger and frustration. The alopecia related global impairment in HRQoL observed in this study [37.44 (28.44 - 57.09)] is similar to alopecia areata (AA) and androgenetic alopecia (AGA) but results in greater emotional impairment [50 (35 - 65)] than either of the two latter diagnoses (AA: 44.6, AGA: 43.8)[30].

Similar to previously published data, we have shown that patients with more advanced skin disease (by mSWAT score and by T-stage) have worse HRQoL[31]. A correlation between mSWAT and overall HRQoL represents a noteworthy finding and this relationship is strengthened in those with confluent erythema indicating that a high burden of skin disease is inextricably linked to worse HRQoL. In ordinal regression analysis of Skindex-29 responses, confluent erythema was associated with more pruritus, irritation and skin sensitivity and resulted in greater functional impairment due to sleep disturbance and difficulty in showing affection. This finding is similar to that observed in patients with psoriasis in whom more extensive disease and specific anatomical involvement experience a greater difficulty with physical intimacy[32].

PROCLIPI provides a unique platform to enhance our understanding of HRQoL in MF/SS patients, in particular by eliminating the single-centre/country bias in previous large studies. It is plausible that a number of limitations may have influenced the results obtained. Firstly, the number of other previously diagnosed medical and psychiatric co-morbidities is not recorded. A recent study found psychiatric condition and medical co-morbidities were significantly related to symptoms[33]. Secondly, the Skindex-29 instrument is a skin disease specific questionnaire and does not contain specific questions relating to cancer. Thirdly, as our study involved newly diagnosed patients, we did not examine the effect of treatment on HRQoL in MF/SS. Systemic therapies may adversely affect HRQoL and therefore future studies to examine the impact of systemic treatment on HRQoL is important especially if patients with MF/SS have a stronger belief in treatment control[19]. This work has highlighted the need to develop a composite MF/SS specific questionnaire which simultaneously examines the effect of both skin disease and cancer diagnosis on HRQoL. A specific MF/SS-CTCL QoL instrument to capture patient HRQoL was recently developed and represents a pivotal step in the right direction to provide more patient-tailored supportive care. However, the sample of patients who participated in this study were largely of those with stage I disease, thus under-representing those with more advanced stages[34].

In conclusion, this study has highlighted important patient-specific and disease-specific features which impact HRQoL in MF/SS patients. Even though male patients may have an overall worse prognosis[1] it is interesting to note an overall worse HRQoL in females. Patients with alopecia and more extensive cutaneous disease experienced worse overall HRQoL with greater emotional, symptomatic and functional impairment. This is highly relevant as treatments in MF/SS rarely result in complete responses and partial responses are only seen in 20-40%[35] meaning most patients

continuously suffer cutaneous disease. Living with a cancer diagnosis and fear of dying can also significantly affect HRQoL. In-depth in-person qualitative interviews may assist in the development of a CTCL specific HRQoL questionnaire that encompasses both early and late-stage disease to enable us to fully understand the impact of HRQoL in MF/SS.

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Table 1. Participating International Centres

Centre No.	Principal Investigator	Address	No. Patients
E001	Julia Scarisbrick	University Hospitals Birmingham, UK	62
E047	Anne Marie Busschots	University Hospitals Leuven, Belgium	20
E012	Constanze Jonak	Medical University of Vienna, Austria	18
E006	Richard Cowan	Christie Hospital, Manchester, UK	17
E007	Evangelina Papadavid	Athens University Medical School, Greece	13
E022	Marie Beylot-Barry	Centre Hospitalier Universitaire Hospital de Bordeaux, France	11
E024	Emilio Berti	Department of Dermatology, Fondazione Ca' Granda, IRCCS, OMP, Milano, Italy	10
E023	Teresa Estrach	Hospital Clinico, University of Barcelona, Spain	9
E028	Rubeta Matin	Churchill Hospital, Oxford, UK	9
E063	Oleg Akilov	University of Pittsburgh School of Medicine, Pennsylvania, USA	9
E017	Liisa Vakeva	Helsinki University Central Hospital, Finland	8
E056	Miles Prince	Peter Maccallum Cancer Centre, Melbourne, Australia	8
E031	Andrew Bates	University Hospital Southampton, UK	7
E013	Emmanuella Guenova	University Hospital Zurich, Switzerland	6

E032	Mike Bayne	Poole Hospital, Dorset, UK	5
E036	Rachel Wachsmuch	Royal Devon & Exeter Hospital, UK	5
E046	Ulrike Wehkamp	University Hospital Kiel, Germany	5
E045	Marta Marschalko	Semmelweis University, Budapest, Hungary	3
E019	Octavio Servitje	Hospital Universatari de Bellvitge, Barcelona, Spain	2
E034	Deborah Turner	Torbay Hospital, UK	2
E037	Sophie Weatherhead	Newcastle Upon Tyne NHS Trust, UK	2
E048	Marion Wobser	University Hospital Wuerzburg, Germany	2
E059	José Antonio Sanches	University of Sao Paulo Medical School, Brazil, South America	2
E039	Pam McKay	Beatson West of Scotland Cancer Centre, Glasgow, Scotland	1
E058	Detlev Klemke	Stadtisches Klinikum Karlsruhe, Germany	1

Table 2. Demographics and Baseline Characteristics of Study Population (n = 237)

Patient Characteristics		
Characteristic	Value	n (%), unless stated otherwise
Age[a]	Median (IQR)	60 (49 - 70)
Gender	Male	143 (60.34)
	Female	94 (39.66)
ECOG	0	214 (90.3)
	1	15 (6.33)
	2	6 (2.53)
	3	2 (0.84)
Skindex-29 Score[a]	Global	29.75 (15.44 - 47.21)
	Symptoms	39.29 (21.43 - 57.14)
	Emotions	35 (20 - 55)
	Functioning	12.5 (4.167 - 33.85)
Disease Characteristics		
Characteristic	Value	n (%), unless stated otherwise
mSWAT Score[a]	-	20 (6.6 – 54.8)
MF/SS	Mycosis Fungoides	211 (89.03)
	Sézary Syndrome	26 (10.97)
Disease Stage	IA	94 (39.66)
	IB	72 (30.38)
	IIA	16 (6.75)
	IIB	18 (7.59)
	IIIA	5 (2.11)
	IIIB	9 (3.8)

	IV (A1)	14 (5.91)
	IV (A2)	7 (2.95)
	IVB	2 (0.84)
Early vs Late-stage	Early	179 (75.53)
	Late	58 (24.47)
Raised LDH	-	53 (22.36)
Alopecia	-	35 (14.77)
Confluent erythema	-	54 (22.78)
Hypopigmentation	-	14 (5.91)
Ulceration	-	15 (6.33)
Follicular MF Lesions	-	45 (18.99)

Notes

[a] Values quoted as median + (IQR, interquartile range)

Abbreviations: ECOG, Eastern Cooperative Oncology Group Performance status; mSWAT, modified Severity Weighted Assessment Tool; MF, mycosis fungoides; LDH, lactate dehydrogenase.

Table 3. Variables associated with worse QoL in patients with MF/SS

		n	Global		Symptoms		Emotions		Functioning	
			Value	P-value	Value	P-value	Value	P-value	Value	P-value
Age[a]	-	237	-0.014	0.83	0.037	0.57	0.081	0.21	-0.0003	0.99
ECOG[b]	0	214	30.24 (15.48 – 46.35)		39.29 (21.43 – 57.14)		35 (20 – 55)		12.5 (4.17 – 33.33)	
	1	15	25.65 (12.78 – 65)	0.23	35.71 (25 – 75)	0.29	25 (12.5 – 45)	0.13	10.42 (6.25 – 60.42)	0.29
	2	6	63.19 (19.43 – 80.87)		51.79 (43.75 – 77.68)		66.25 (11.3 – 87.5)		64.58 (3.13 – 80.21)	
	3	2	17.27 (12 – 22.54)		30.36 (21.43 – 39.29)		16.25 (12.5 – 20)		5.2 (2.1 – 8.3)	
Gender	Males	143	27.62 (13.73 - 44.87)	0.02	35.71 (17.86 - 53.57)	0.01	30 (17.5 - 52.5)	0.02	12.5 (2.08 - 29.69)	0.12
	Females	94	34.19 (20.69 - 52.84)		42.86 (25 - 64.29)		40 (23.12 - 59.38)		15.62 (6.25 - 37.5)	
mSWAT[a]	-	237	0.3514	<0.0001	0.3812	<0.0001	0.263	<0.0001	0.3286	<0.0001
MF/SS	MF	211	28.46 (14.67 - 44.87)	0.001	35.71 (17.86 - 53.57)	0.0003	32.5 (19.38 - 52.5)	0.05	12.5 (2.08 - 29.17)	0.001
	SS	26	50.58 (27.21 - 69.53)		55.36 (42.86 - 75)		45 (27.5 - 72.5)		40.63 (8.85 - 61.98)	
Disease Stage	Early	179	27.55 (14.67 - 42.43)	0.002	35.71 (17.86 - 53.57)	0.0002	32.5 (20 - 52.5)	0.09	12.5 (2.08 - 29.17)	0.002
	Late	58	36.46 (21.94 - 65.83)		50 (35.71 - 71.43)		42.5 (20 - 71.25)		20.83 (8.33 - 59.9)	
Raised LDH	No	184	27.48 (14.64 - 43.04)	0.001	35.71 (17.86 - 50)	<0.0001	32.5 (20 - 52.5)	0.05	12.5 (4.17 - 29.17)	0.002
	Yes	53	36.35 (24.56 - 68.53)		53.57 (35.71 - 75)		40 (20 - 72.5)		22.92 (8.33 - 60.42)	
Alopecia	No	202	27.62 (13.89 - 45.91)	0.004	39.29 (17.86 - 57.14)	0.05	30 (17.5 - 52.5)	0.001	12.5 (3.13 - 31.25)	0.03

	Yes	35	37.44 (28.44 - 57.09)		42.86 (30.36 - 64.29)		50 (35 - 65)		22.92 (9.38 - 57.29)	
Confluent erythema	No	183	26.37 (14.67 - 42.43)	0.001	35.71 (17.86 - 50.89)	<0.0001	32.5 (19.38 - 52.5)	0.11	10.42 (2.08 - 29.17)	0.0007
	Yes	54	36.51 (26.3 - 64.33)		53.57 (36.61 - 70.54)		40 (22.5 - 65)		26.04 (8.85 - 57.81)	
Hypopigmentation	No	223	29.8 (15.78 - 47.28)	0.65	39.29 (21.43 - 57.14)	0.13	35 (20 - 52.5)	0.70	12.5 (4.17 - 33.33)	0.88
	Yes	15	26.53 (13.27 - 43.04)		25 (8.93 - 42.86)		42.5 (18.75 - 55)		12.5 (5.21 - 34.38)	
Ulceration	No	222	29.7 (15.41 - 46.18)	0.26	39.29 (21.43 - 57.14)	0.08	35 (20 - 52.5)	0.70	12.5 (4.17 - 33.33)	0.39
	Yes	15	34.84 (23.55 - 60.2)		46.43 (41.07 - 71.43)		35 (21.25 - 62.5)		14.58 (6.25 - 58.33)	
Follicular MF	No	192	33.47 (29.31 - 95.48)	0.73	39.69 (39.29 - 96.43)	0.81	37.97 (32.5 - 100)	0.54	22.77 (12.5 - 100)	0.88
	Yes	45	35.42 (31.29 - 100)		41.59 (39.29 - 100)		40.56 (37.5 - 100)		24.12 (14.58 - 100)	0.99

Notes: Results analysed using the Mann-Whitney U test unless otherwise indicated

[a]Analysed using the non-parametric Spearman's rank-order correlation

[b]Analysed using the Kruskal-Wallis test, with Bonferroni correction for multiple comparisons

Abbreviations: MF, mycosis fungoides; SS, Sézary syndrome

Table 4. Multiple linear regression analysis of factors influencing Skindex-29 scores in patients with MF/SS.

Variable	n	Global			Symptoms			Emotions			Functioning		
		β	SE	P-value	β	SE	P-value	β	SE	P-value	β	SE	P-value
Age	-	-0.06	0.09	0.48	-0.04	0.09	0.67	-0.11	0.10	0.28	-0.04	0.10	0.71
Female Gender	94	8.61	2.84	0.003**	9.95	3.07	0.001**	9.08	3.20	0.005**	6.80	3.17	0.03*
Sézary Syndrome	26	6.65	5.89	0.26	6.44	6.36	0.31	4.30	6.65	0.52	9.21	6.57	0.16
Late-stage Disease	58	4.87	4.21	0.25	5.24	4.55	0.25	4.53	4.76	0.34	4.83	4.70	0.31
Alopecia	35	9.71	4.00	0.02*	8.43	4.32	0.05	12.70	4.52	0.01**	8.02	4.47	0.07
Confluent Erythema	54	8.13	4.08	0.05	10.95	4.40	0.01**	3.66	4.60	0.43	9.77	4.55	0.03*

Note: Linear regression co-efficient (β) with standard errors (SE), where significance codes: * $p<0.05$; ** $p\leq0.01$.

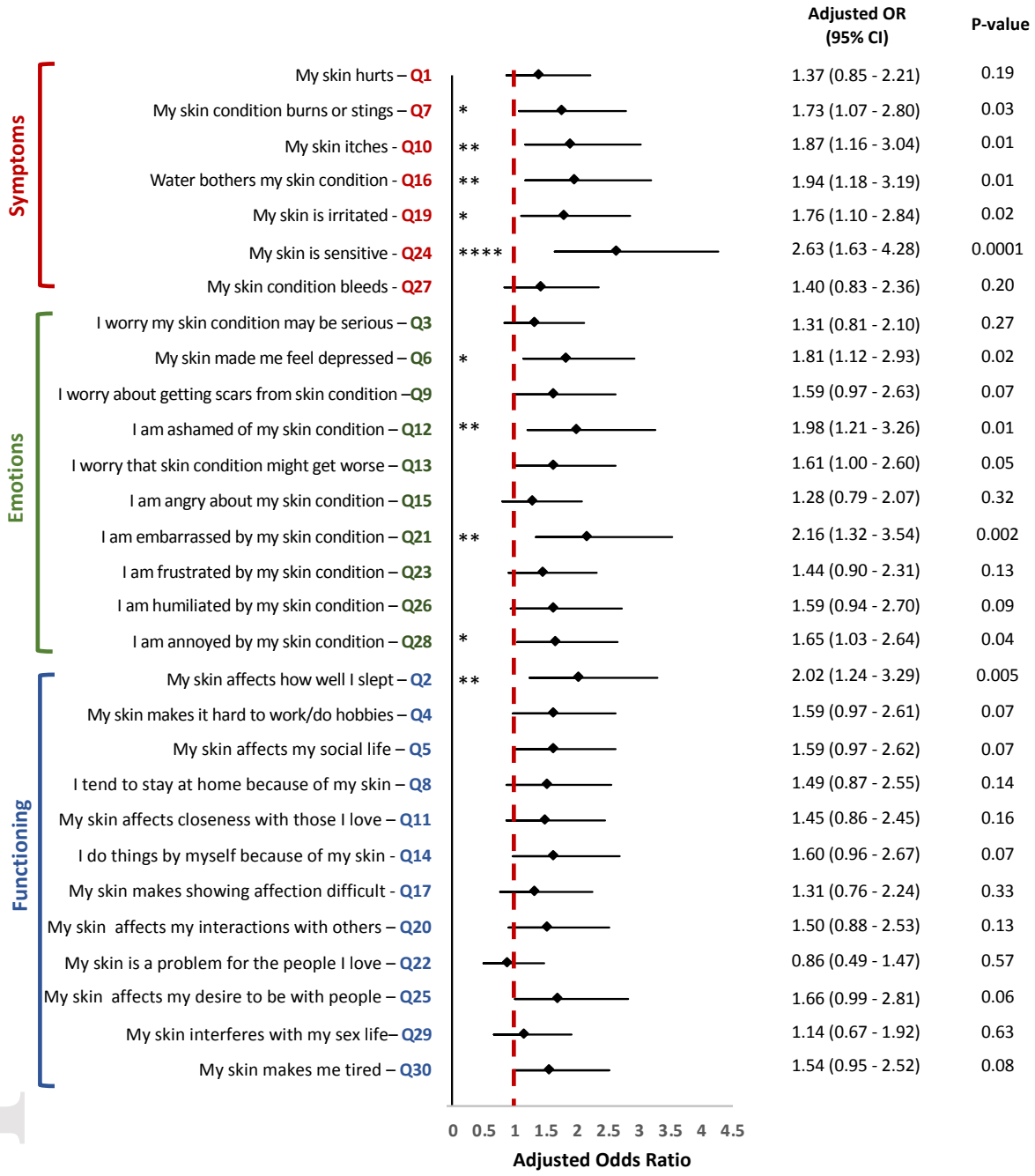

Figure 1. Item-level analysis on the effect of female gender on Skindex-29 responses. The main effect of gender on Skindex-29 responses was analysed using ordinal regression analysis by controlling for age, MF/SS, early/late-stage disease, alopecia and confluent erythema. Results are adjusted odds ratio (OR) and 95% confidence interval (CI), where significance codes: * p<0.05; **

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